II. REMARKS

Preliminary Remarks

Claims 38, 39, 44, 51, 56, 61-63, 65, 67-70, 72-75, 78-80, 83, 86, 94, 99, 100, 102-105, 107, 108, 110-115, 118, and 119 and 126 are currently amended. Claims 40, 52, 53, 71, 81, 82, 106, 120, 124 and 125 are newly canceled, and new claims 129-141 are added.

Upon entry of the amendment, claims 38, 39, 42, 44-51, 56-63, 65, 67-70, 72-75, 78-80, 83, 84, 86-92, 94-100, 102-105, 107, 108, 110-116, 118, 119, 121-123, and 126-141 will be pending in this application.

Independent claims 38, 61, 83, and 99 are amended in step (a) to specify administering a combination of luteinizing hormone (LH) and follicle stimulating hormone (FSH) to induce follicle growth, support for which is found in the specification in the description of administering "exogenous gonadotropins" to induce follicle growth (*e.g.*, on page 3, line 21), and the description of administering HMG to induce follicle growth, (*e.g.*, on page 5, line 18, and Table II), which persons of skill in the art would know comprises a combination of LH and FSH as the active components that induce follicle growth.

Independent claims 38, 61, 83, 99, and 115 are amended in step (b) to specify administering a a luteinizing hormone releasing hormone (LHRH) antagonist selected from the group consisting of Ganirelix, Antarelix, Antide, Azaline B, Ramorelix, A-76154, Nal-Glu, 88-88, Cetrorelix, D-23980, and D-24824, *e.g.*, as described on page 5, lines 2-3, of the specification.

Claims 39, 70 and 105, which depend on claims 38, 61, and 99, respectively, are amended to specify, and new claim 139, which depends on claim 83, similarly specifies, that step (a) comprises administering human menopausal gonadotropin (HMG) to induce follicle growth. that step (a) comprises administering human menopausal gonadotropin (HMG) to induce follicle growth, as described in the specification, *e.g.*, on page 5, line 18, and Table II, as noted above.

Independent claims 38 and 51 are further amended to specify that the LHRH antagonist is administered in a dosage regimen of 3 mg per dose, as described in the specification, *e.g.*, on page 10, lines 4-6.

Independent claim 99 is further amended to specify that the LHRH antagonist is administered in a dosage regimen of daily doses of from 0.25 to 0.5 mg/day for multiple days, support for which is found in the specification, *e.g.*, on page 6 (describing administering multiple doses of 0.25 mg or higher) and in Table I on page 7 (describing administering multiple doses of 0.25 and 0.5 mg/day, with 0.25 mg/day described as the minimum effective dose for multiple dosing).

Independent claims 61 and 99 are further amended to be directed to a method wherein ovulation occurs normally between day 9 and 20 of the menstruation cycle without the administration of a hormone or hormone agonist to induce ovulation. This amendment incorporates the subject matter of previous dependent claims 70 and 105 into claims 61 and 99, respectively.

Claims 73 and 108 are amended to depend on amended claims 70 and 105, respectively, which specify administering HMG to induce follicle growth, and are further amended to omit repetitive text.

Claims 44, 56, 67, 78, 86, 94, 102, 110 and 118 are amended by adding the word "on" after the word "starting" for greater clarity.

Claims 61-63, 65, 67-70, 72-75, 78-80, 99, 100, 102-105, 107, 108 and 110-114 are amended by deleting reference to the claimed method being an "improved" method.

Claim 119, which depends on claim 115, is amended to specify a method that is performed on a patient in whom follicular growth is inadequate due to previous treatment with an LHRH antagonist, and wherein step (a) of claim 115 comprises allowing normal follicular growth and development to proceed in the absence of treatment of the patient with an LHRH antagonist and in the absence of stimulation by an exogenous gonadotropin, as described in the specification, *e.g.*, on page 3, lines 22-27.

Claim 126 is amended to depend on claim 115.

New claims 129-138 also depend on claim 115. New claims 129-133 specify features of the disclosed method wherein the LHRH antagonist is administered in a single or dual dosage regimen of 1 to 10 mg per dose, and new claims 134-138 specify features of the disclosed

method wherein the LHRH antagonist is administered in a dosage regimen of daily doses of from 0.25 to 0.5 mg/day for multiple days.

New claims 140 and 141 depend respectively on claims 99 and 108, and specify that Cetrorelix is administered for multiple days in a dosage regimen of daily doses of 0.25 or 0.5 mg/day, as described, for example, in Table I on page 7, as noted above.

The applicant does not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserves the right to pursue such subject matter in continuing applications.

Reconsideration and allowance of the present application based on the above-described amendments and the following remarks are respectfully requested.

Patentability Remarks

35 U.S.C. §112, First Paragraph / Enablement

A. Claims 38-40, 44-50, 61-63, 65, 67-72, 83-84, 86-91, 99-100, 102-107, 115-116 and 118-128 are rejected under 35 U.S.C. §112, first paragraph, because the specification is considered to be enabling for the claimed methods wherein HMG is administered to induce follicle growth, and wherein Cetrorelix is administered as the LHRH antagonist, but allegedly does not enable the claimed methods wherein follicle growth is induced by administering "exogenous gonadotropins," and wherein the LHRH antagonist is not identified. Pending claim 42 is not listed as a rejected claim, however, the applicants' response also applies to claim 42.

The examiner alleges that undue experimentation would have been required to practice the claimed methods because the term "exogenous gonadotropins," encompasses human chorionic gonadotropin (hCG) and thyroid stimulating hormone (TSH), and LH alone, and one of skill in the art at the time the application was filed allegedly would not have known how to administer TSH, hCG, or LH alone to induce follicle growth in a method of COS/ART.

The examiner further argues that the term "LHRH antagonist" encompasses non-functional LHRH antagonists and LHRH antagonists that have not yet been discovered, and that undue experimentation would have been required by one of skill in the art at the time of filing to "determine all the functioning antagonistic analogs of LHRH" in order to practice the claimed methods. The examiner cites Griesinger *et al.* (2004) as teaching that as of 2004, "only two LHRH antagonists were commercially available for prevention of premature LH surges in ovarian stimulation, namely Cetrorelix and Ganirelix." *See* pages 2-4 of the official action.

The applicants respectfully disagree with the examiner's position that the specification does not enable one of skill in the art to practice the methods of the rejected claims successfully without having to perform undue experimentation. However, in order to expedite prosecution of the present application, independent claims 38, 61, 83, 99, and 115 are amended. Specifically, step (a) of claims 38, 61, 83, and 99 is amended to specify that follicle growth is induced by administering a combination of LH and FSH, which were recognized at the time of filing by persons of skill in the art as gonadotropins that are present in HMG that can be administered as exogenous gonadotropins to induce follicle growth as described in the application. In addition, step (b) of claims 38, 61, 83, 99, and 115 is amended to specify administering an LHRH antagonist selected from the group consisting of Ganirelix, Antarelix, Antide, Azaline B, Ramorelix, A-76154, Nal-Glu, 88-88, Cetrorelix, D-23980, and D-24824, which are described on page 5, lines 2-3, of the specification. The applicants submit that undue experimentation would not have been required to practice the claimed method successfully, despite the lack of commercial availability and/or clinical utilization of all of the disclosed LHRH antagonists at the time of filing, according to Griesinger et al. The structures and methods for preparing the disclosed LHRH antagonists specified in the amended claims, and their LHRH antagonistic activities *in vivo* were well known by persons of skill in the art at the time the application was filed. For example, see the attached abstracts of Nelson et al. (Fertil. Steril., 1995, 63:963-9), Rivier et al. (Biochem. Biophys. Res. Comm., 1991, 176:406-12), Baril et al. (Theriogenology, 1996, 45:6970706), Dubourdieu et al. (J. Clin. Endocrinol. Metab., 1994, 78:343-7), and Haviv et al. (J. Med. Chem., 1994, 37:701-5), describing *in vivo* LHRH antagonistic activities of Ganirelix, Azaline, Antarelix, Nal-Glu and A-76154, respectively. Methods for determining the dosage of an LHRH antagonist that prevents LH surge *in vivo* during a COS/ART protocol were

also known at the time of filing. Accordingly, the applicants respectfully submit that at the time of filing, one of skill in the art would have been able to successfully practice the method for obtaining the production of a fertilizable oocyte within a program of COS/ART according to the amended claims without having to perform undue experimentation. As discussed above, one of skill in the art at the time of filing would have known how to induce follicle growth by administering a combination of LH and FSH as specified in step (a) of the claimed method, without difficulty or undue experimentation. One of skill in the art at the time of filing would also have been able to obtain or prepare the LHRH antagonists disclosed in the specification and specified in step (b) of the claimed method, the structures and *in vivo* activities of which were well-known at the time of filing, and use them in the claimed method to suppress premature LH surges, also without undue difficulty or experimentation. Withdrawal of the rejection of claims 38-40, 44-50, 61-63, 65, 67-72, 83-84, 86-91, 99-100, 102-107, 115-116 and 118-128 under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

B. The examiner further rejects claims 83-128 under 35 U.S.C. §112, first paragraph, for alleged failure to comply with the enablement requirement, because the specification allegedly does not enable one of skill in the art to successfully practice the claimed methods wherein the LHRH antagonist is administered in a dosage regimen of daily doses of 0.25 mg/day for multiple days. In support of this ground of rejection, the examiner cites Tavanioutov *et al.* (2003) and Engel *et al.* (2002) as teaching that COS/ART methods in which an LHRH antagonist is administered in multiple daily doses of 0.25 mg/day may be associated with increased number of premature LH surges, lower fertilization rates in IVF, and increased embryonic loss, compared to methods wherein higher dosages of an LHRH antagonist are administered. The examiner also cites Felberbaum *et al.* (1996) as teaching that at the time of filing, the minimal effective dosage of Cetrorelix per day was undefined. *See* pages 5-7 of the official action.

The applicants submit that the application clearly describes the claimed method wherein LHRH antagonist is administered in a dosage regimen of daily doses of 0.25 mg/day for multiple days in a manner that enables one of skill in the art to practice the claimed method successfully without having to perform undue experimentation. For example, page 6 of the application describes performing a method for COS/ART in which "multiple doses of 0.25 mg or higher" of

Cetrorelix are administered to prevent premature LH surge, and Table I on page 7 shows the results of a working example wherein Cetrorelix was administered in a dosage regimen of daily doses of 0.1, 0.25, and 0.5 mg/day for multiple days, and indicates that 0.25 mg/day was determined to be the minimum effective dosage for daily administration for multiple days. General procedures of COS/ART were well known at the time of filing, and one of skill in the art would read and understand the teachings of the present application in the context of his or her considerable experience and knowledge regarding COS/ART methodology. Moreover, Griesinger *et al.* (2004, cited by the examiner) teaches that COS/ART treatment regimens in which multiple doses 0.25 mg/dose of cetrorelix or ganirelix are administered to prevent premature LH surges yield results that are comparable in terms of efficacy and safety with a single-dose protocol in which a 3 mg dose of cetrorelix is administered. *See* page 565, lower right column. COS/ART treatments resulting in successful pregnancies in which multiple doses of 0.25 mg/dose of cetrorelix are administered are also described by Duijkers et al. (Human Reprod., 1998, 13:2392-8, *see* page 2397), Albano et al. (Fertil. Steril., 1997, 67:917-22, abstract only), Felberbaum et al. (Human Reprod., 2000, 15:1015-20, abstract only), and Huirne et al. (Human Reprod., 2006, 21:1408-15, abstract only), copies of which are attached. The present application and the published scientific literature clearly demonstrate that the claimed method for obtaining the production of a fertilizable oocyte within a program of COS/ART wherein multiple doses of 0.25 mg/dose of LHRH antagonist are administered to prevent premature LH surges can be performed successfully. Accordingly, undue experimentation would not have been required for one of skill in the art to successfully practice the claimed method as described by the present application, and withdrawal of the rejection of claims 83-128 under 35 U.S.C. §112, first paragraph, for alleged failure to comply with the enablement requirement, is respectfully requested.

35 U.S.C. §102(b)

A. Olivennes *et al.*

Claims 38, 39, 42, 45, 46, 48-52, 56-58, 60-62, 65, 67-69, 71-74, 78-80 and 82 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Olivennes *et al.* (Fertil. Steril., 1994). Olivennes *et al.* describe a method for obtaining the production of a fertilizable oocyte within a program of COS/ART comprising (a) administering HMG to induce follicle growth, and (b) administering cetrorelix in a single or dual dosage regimen of 5 mg per dose to prevent a premature LH surge, wherein the first dose of cetrorelix was administered when plasma estradiol levels were between 150 and 200 pg/ml per follicle of ≥ 14 mm, which occurred on average on day 9.6 ± 0.6 of the cycle. *See* page 469, paragraph 3 of the Study Protocol, and page 470, paragraph 1 of the Results. The method described by Olivennes *et al.* further comprises administering hCG to induce ovulation when the leading follicle attained 18-20 mm and estradiol levels were > 920 pmol/ml per follicle. *See* page 469, paragraph 4 of the Study Protocol.

The applicants respectfully submit that the claims of the present application are directed to a method that is different from and is not anticipated by the method described by Olivennes *et al.*

To anticipate a claim, a reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). See the Manual for Patent Examining Procedure (M.P.E.P.), §2131.

Pending claims 38, 39, 42, 45, 46, 48-51, 56-58 and 60 are not anticipated by Olivennes *et al.*

Independent claims 38 and 51 are amended to be directed to a method for obtaining the production of a fertilizable oocyte within a program of COS/ART comprising (a) administering LH and FSH to induce follicle growth, and (b) administering an LHRH antagonist in a single or

dual dosage regimen of 3 mg per dose, beginning on cycle day 1 to 10, to prevent a premature LH surge. Please note that rejected claim 52 is canceled.

Olivennes *et al.* do not describe a method comprising administering an LHRH antagonist in a single or dual dosage regimen of 3 mg per dose, beginning on cycle day 1 to 10, to prevent a premature LH surge. Accordingly, claims 38 and 51, and pending claims 39, 42, 45, 46, and 48-50, 56-58 and 60 that depend on claims 38 and 51, are not anticipated by Olivennes *et al.* under 35 U.S.C. §102(b).

Pending claims 61, 62, 65, 67-69, 72-74, and 78-80 are not anticipated by Olivennes *et al.*

Independent claim 61 is amended to be directed to a method for obtaining the production of a fertilizable oocyte within a program of COS/ART comprising (a) administering LH and FSH to induce follicle growth, and (b) administering an LHRH antagonist in a single or dual dosage regimen of 1 to 10 mg per dose, beginning on cycle day 1 to 10, to prevent a premature LH surge, wherein ovulation occurs normally between day 9 and 20 of the menstruation cycle without the administration of a hormone or hormone agonist to induce ovulation. Please note that rejected claims 71 and 82 are canceled.

Olivennes *et al.* describe a method comprising administering hCG to induce ovulation when the leading follicle is 18-20 mm in diameter, as discussed above. Olivennes *et al.* do not describe the method of the claimed invention wherein ovulation occurs normally between day 9 and 20 of the menstruation cycle without the administration of a hormone or hormone agonist to induce ovulation. Accordingly, claim 61 and pending claims 62, 65, 67-69, 72-74, and 78-80 that depend on claim 61, are not anticipated by Olivennes *et al.* under 35 U.S.C. §102(b).

In view of the foregoing, withdrawal of the rejection of claims 38, 39, 42, 45, 46, 48-51, 56-58, 60-62, 65, 67-69, 72-74, and 78-80 under 35 U.S.C. §102(b) as allegedly being anticipated by Olivennes *et al.* is respectfully requested.

B. Diedrich *et al.*

Claims 38, 39, 40, 42, 44-46, 48-53, 56-58, 60-63, 65, 67, 68, 71-75, 78-80 and 82 are rejected under 35 U.S.C. 102(b) as being anticipated by Diedrich *et al.* (Hum Reprod. 1994). Diedrich *et al.* describe a method for obtaining the production of a fertilizable oocyte within a

program of COS/ART comprising (a) administering HMG to induce follicle growth, and (b) administering cetrorelix in a dosage regimen of multiple daily doses of 3 mg/day to prevent a premature LH surge, wherein the first daily dose of cetrorelix was administered on day 7 of the cycle, and daily treatment continued until ovulation was induced by administration of HCG when the leading follicle reached a diameter of 18-20 mm and plasma estradiol levels were > 300 pg/ml per follicle of ≥ 15 mm in diameter. Diedrich *et al.* also describe performing the same method wherein cetrorelix is administered in a dosage regimen of multiple daily doses of 1 mg/day. *See* page 788, left column, and page 789, paragraph 2 of Materials and methods. As shown in Figures 1 and 2 on page 789, daily doses of cetrorelix were administered from day 7 until ovulation was induced on day 14 or day 15 of the cycle.

The applicants respectfully submit that the claims of the present application are directed to a method that is different from and is not anticipated by the method described by Diedrich *et al.*

As stated above, to anticipate a claim, a reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Citations omitted; *see* above, and Manual for Patent Examining Procedure (M.P.E.P.), §2131.

Pending claims 38, 39, 42, 44-46, 48-51, and 56-58 are not anticipated by Diedrich *et al.*

Independent claims 38 and 51 are amended to be directed to a method for obtaining the production of a fertilizable oocyte within a program of COS/ART comprising (a) administering LH and FSH to induce follicle growth, and (b) administering an LHRH antagonist in a single or dual dosage regimen of 3 mg per dose, beginning on cycle day 1 to 10, to prevent a premature LH surge. Please note that rejected claims 40, 52, and 53 are canceled.

Diedrich *et al.* describe a method wherein cetrorelix is administered in a dosage regimen of multiple daily doses of 3 mg/day starting on day 7 of the cycle and continuing until ovulation was induced on about day 14 or day 15 of the cycle, in order to prevent a premature LH surge, as discussed above. Diedrich *et al.* do not describe a method comprising administering an LHRH antagonist in a single or dual dosage regimen of 3 mg per dose to prevent a premature LH surge.

Accordingly, claims 38 and 51, and pending claims 39, 42, 44-46, 48-50, 56-58 and 60 that depend on claims 38 and 51, are not anticipated by Diedrich *et al.* under 35 U.S.C. §102(b).

Pending claims 61-63, 65, 67, 68, 72-75, and 78-80 are not anticipated by Diedrich *et al.*

Independent claim 61 is amended to be directed to a method for obtaining the production of a fertilizable oocyte within a program of COS/ART comprising (a) administering LH and FSH to induce follicle growth, and (b) administering an LHRH antagonist in a single or dual dosage regimen of 1 to 10 mg per dose, beginning on cycle day 1 to 10, to prevent a premature LH surge, wherein ovulation occurs normally between day 9 and 20 of the menstruation cycle without the administration of a hormone or hormone agonist to induce ovulation. Please note that rejected claims 71 and 82 are canceled.

Diedrich *et al.* describe a method wherein ovulation was induced by administration of HCG when the leading follicle reached a diameter of 18-20 mm, as discussed above. Diedrich *et al.* do not describe the method of the claimed invention wherein ovulation occurs normally between day 9 and 20 of the menstruation cycle without the administration of a hormone or hormone agonist to induce ovulation. Accordingly, claim 61 and pending claims 62, 63, 65, 67, 68, 72-75, and 78-80 that depend on claim 61, are not anticipated by Diedrich *et al.* under 35 U.S.C. §102(b).

In view of the foregoing, withdrawal of the rejection of claims 38, 39, 42, 44-46, 48-51, 56-58, 61-63, 65, 67, 68, 72-75, and 78-80 under 35 U.S.C. §102(b) as allegedly being anticipated by Diedrich *et al.* is respectfully requested.

Obvious-Type Double Patenting Rejection

Claims 38-39, 42, 45-52, 56-62, 65, 67-74, 78-82, 86-92, 94-100, 102-108, 110-116 and 118-128 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22, 26-42 of co-pending U.S. Application No. 10/661,780. The claims of Application No. 10/661,780 are directed to a method of treating infertility disorders that comprises inducing follicle growth by administration of hMG or recombinant FSH in combination with clomiphene, which method is considered to be

encompassed by the claims of the present application. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The applicant will consider submitting a terminal disclaimer once there is indication of allowable subject matter in the present application or in co-pending Application No. 10/661,780.

III. CONCLUSION

In view of the foregoing, the applicants believe that the claims are in form for allowance, and hereby respectfully solicit such action. If any point remains in issue which the examiner feels may be best resolved through a personal or telephone interview, the examiner is strongly urged to contact the undersigned at the telephone number listed below.

Respectfully submitted,

/ thomas a cawley jr /

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